AMENDMENTS TO THE CLAIMS

1. (Previously Presented) A lipid-based drug delivery system for administering an active lysolipid drug substance, which is not a substrate for lysophospholipase, to tissues expressing increased levels of extracellular phospholipase A2, comprising:

(a) A prodrug lipid derivative having:

(1) An alkyl-linked aliphatic group of a length of at least 7 carbon atoms;

(2) An acyl-linked organic radical having at least 7 carbon atoms, and

(3) A hydrophilic moiety, and

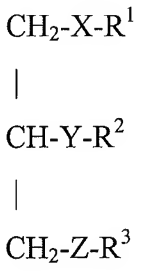
(b) At least one lipopolymer or glycolipid

2. (Previously Presented) The drug delivery system according to claim 1, wherein the lipopolymers or glycolipids are represented by at least a fraction of the prodrug lipid derivative.

3. (Previously Presented) The drug delivery system according to claim 1, wherein the polymer of the lipopolymer is selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatised celluloses.

4. (Previously Presented) The drug delivery system according to claim 1, wherein the organic radical is an auxiliary drug substance or an efficiency modifier for the active drug substance.

5. (Previously Presented) The drug delivery system according to claim 1, wherein the prodrug is a lipid derivative of the following formula:



wherein
X and Z independently are selected from O, CH_2, NH, NMe, S, S(O), and $S(O)_2$;

Y is -OC(O)-, Y then being connected to R^2 via either the oxygen or carbonyl carbon atom;

R^1 is an aliphatic group of the formula Y^1Y^2;

R^2 is an organic radical having at least 7 carbon atoms;

where Y^1 is $-(CH_2)_{n1}-(CH=CH)_{n2}-(CH_2)_{n3}-(CH=CH)_{n4}-(CH_2)_{n5}-(CH=CH)_{n6}-(CH_2)_{n7}-(CH=CH)_{n8r}-(CH_2)_{n9}$, and the sum of n1+2n2+n3+2n4+n5+2n6+n7+2n8+n9 is an integer of from 9 to 29; n1 is zero or an integer of from 1 to 29, n3 is zero or an integer of from 1 to 20, n5 is zero or an integer of from 1 to 17, n7 is zero or an integer of from 1 to 14, and n9 is zero or an integer of from 1 to 11; and each of n2, n4, n6 and n8 is independently zero or 1; and Y^2 is CH_3 or CO_2H; where each Y^1-Y^2 independently may be substituted with halogen or C_{1-4}-alkyl,

R^3 is selected from phosphatidic acid (PO_2-OH), derivatives of phosphatidic acid and bioisosters to phosphatic acid and derivatives thereof.

6. (Previously Presented) The drug delivery system according to claim 5, wherein R^2 is an aliphatic group of a length of at least 7 carbon atoms.

7. (Previously Presented) The drug delivery system according to claim 6, wherein R^2 is a group of the formula Y^1Y^2.

8. (Previously Presented) The drug delivery system according to claim 1, wherein at least a fraction of the prodrug lidid derivative is of the formula defined in claim 5, wherein R^3 is a derivative of phosphatidic acid to which a polymer selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatised celluloses, is covalently attached.

9. (Previously Presented) The drug delivery system according to claim 1, wherein the prodrug lipid derivative constitutes 15-100 mol% of the total dehydrated lipid-based system.

10. (Previously Presented) The drug delivery system according to claim 1, wherein the lipopolymer constitutes 1-50 mol% of the total dehydrated system.

11. (Previously Presented) The drug delivery system according to claim 1, wherein the lipid-based system is in the form of liposomes .

12. (Previously Presented) The drug delivery system according to claim 1, which is in the form of liposomes wherein a second drug substance is incorporated.

13. (Previously Presented) A drug delivery system according to claim 12, wherein the second drug substance is a therapeutically and/or prophylactically active substance selected from the group consisting of (i) antitumor agents , (ii) antibiotics and antifungals, and (iii) antiinflammatory agents.

14. (Original) A pharmaceutical composition comprising the lipid-based drug delivery system according to claim 1 and optionally a pharmaceutically acceptable carrier.

15. (Previously Presented) A method for selectively drug targeting to neoplastic cells within a mammalhaving an extracellular phospholipase A2 activity which is at least 25% higher compared to the normal activity in said areas, by administering to the mammal in need thereof an efficient amount of the lipid-based drug delivery system according to claim 1.

16. (Previously Presented) A method of treating a mammalby administering to the mammal in need thereof an efficient amount of the lipid-based drug delivery system according to claim 1.

17. (Previously Presented) The method according to claim 16 for the treatment of diseases or conditions associated with a localized increase in extracellular phospholipase A2 activity in mammalian tissue.

18. (Original) The method according to claim 17, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions and cancer.

19. (Original) The method according to claim 18, wherein the type of cancer is selected from the group consisting of brain cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, leukemia, lymphoma, sarcoma and carcinoma.

20. (Previously Presented) The method according to claim 15, wherein the increase in extracellular phospholipase A2 activity is at least 25% compared to the normal level of activity in the tissue in question.

21. (Previously Presented) A method according to claim 20, wherein the lipid-based drug delivery system becomes localized in a diseased tissue after administration and which, after

degradation by extracellular phospholipase A2, leads to an increase in membrane permeability of cells in the diseased tissue.

22. (Previously Presented) The method according to claim 20, wherein the lipid-based drug delivery system includes a second drug substance, a membrane component, and/or an auxiliary drug substance which acts as an proactivator for extracellular phospholipase A2.

23. (Previously Presented) The method according to claim 20, wherein the lipid-based drug delivery system becomes localized in a diseased tissue after administration, and wherein degradation of the lipid-based drug delivery system by extracellular phospholipase A2 in the diseased tissue is accelerated by a localized increase in temperature in said tissue.

24. (Original) The method according to claim 15 for the treatment of diseases or conditions selected from the group consisting of inflammatory conditions and cancer.

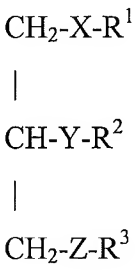
25. (Previously Presented) A lipid-based drug delivery system for administration of an second drug substance, wherein the second drug substance is incorporated in the system, said system including lipid derivatives which has (a) an aliphatic group of a length of at least 7 carbon atoms and an organic radical having at least 7 carbon atoms, and (b) a hydrophilic moiety, where the lipid derivative furthermore is a substrate for extracellular phospholipase A2 to the extent that the organic radical can be hydrolytically cleaved off, whereas the aliphatic group remains substantially unaffected, so as to result in an organic acid fragment or an organic alcohol fragment and a lysolipid fragment, said lysolipid fragment not being a substrate for lysophospholipase, said system having included therein lipopolymers or glycolipids so as to present hydrophilic chains on the surface of the system.

26. (Previously Presented) The drug delivery system according to claim 25, wherein the lipopolymers or glycolipids are represented by at least a fraction of the prodrug.

27. (Previously Presented) The drug delivery system according to claim 25, wherein the polymer of the lipopolymer is selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatised celluloses.

28. (Previously Presented) The drug delivery system according to claim 25, wherein the organic radical which can be hydrolytically cleaved off, is an auxiliary drug substance or an efficiency modifier for the second drug substance.

29. (Previously Presented) The drug delivery system according to claim 25, wherein the lipid derivative is a lipid derivative of the following formula:



wherein
X and Z independently are selected from O, CH_2, NH, NMe, S, S(O), and $S(O)_2$;

Y is -OC(O)-, Y then being connected to R^2 via either the oxygen or carbonyl carbon atom;

R^1 is an aliphatic group of the formula Y^1Y^2;

R^2 is an organic radical having at least 7 carbon atoms;

where Y^1 is $-(CH_2)_{n1}-(CH=CH)_{n2}-(CH_2)_{n3}-(CH=CH)_{n4}-(CH_2)_{n5}-(CH=CH)_{n6}-(CH_2)_{n7}-(CH=CH)_{n8r}-(CH_2)_{n9}$, and the sum of n1+2n2+n3+2n4+n5+2n6+n7+2n8+n9 is an integer of from 9 to 29; n1 is zero or an integer of from 1 to 29, n3 is zero or an integer of from 1 to 20, n5 is zero or an integer of from 1 to 17, n7 is zero or an integer of from 1 to 14, and n9 is zero or an integer of from 1 to 11; and each of n2, n4, n6 and n8 is independently zero or 1; and Y^2 is CH_3 or CO_2H; where each Y^1-Y^2 independently may be substituted with halogen or C_{1-4}-alkyl,

R^3 is selected from phosphatidic acid (PO_2-OH), derivatives of phosphatidic acid and bioisosters to phosphatic acid and derivatives thereof.

30. (Previously Presented) The drug delivery system according to claim 29, wherein R^2 is an aliphatic group of a length of at least 7 carbon atoms.

31. (Previously Presented) The drug delivery system according to claim 30, wherein R^2 is a group of the formula Y^1Y^2.

32. (Previously Presented) The drug delivery system according to claim 25, wherein at least a fraction of the prodrug is of the formula defined in claim 29, wherein R^3 is a derivative of phosphatidic acid to which a polymer selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatized celluloses, is covalently attached.

33. (Previously Presented) The drug delivery system according to claim 25, wherein the lipid derivative constitutes 15-100 mol% of the total dehydrated system.

34. (Previously Presented) The drug delivery system according to claim 25, wherein the lipopolymer constitutes 1-50 mol% of the total dehydrated system.

35. (Previously Presented) The drug delivery system according to claim 25, wherein the system is in the form of liposomes.

36. (Previously Presented) The drug delivery system according to claim 25, wherein the second drug substance is a therapeutically and/or prophylactically active substance selected from (i) antitumor agents, (ii) antibiotics and antifungals, and (iii) antiinflammatory agents.

37. (Original) A pharmaceutical composition comprising the drug delivery system according to claim 25 and optionally a pharmaceutically acceptable carrier.

38. (Previously Presented) A method for selectively drug targeting to neoplastic cells to areas within a mammalian body having a extracellular phospholipase A2 activity which is at least 25% higher compared to the normal activity in said areas, by administering to the mammal in need thereof an efficient amount of the drug delivery system defined in claim 25.

39. (Previously Presented) A method of treating a mammal by administering to the mammal in need thereof an efficient amount of the drug delivery system defined in claim 25.

40. (Previously Presented) The method according to claim 39 for the treatment of diseases or conditions associated with a localized increase in extracellular phospholipase A2 activity in mammalian tissue.

41. (Original) The method according to claim 40, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions and cancer.

42. (Original) The method according to claim 41, wherein the type of cancer is selected from the group consisting of brain cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, leukemia, lymphoma, sarcoma and carcinoma.

43. (Original) The method according to claim 38, wherein the increase in extracellular phospholipase A2 activity is a least 25% compared to the normal level of activity in the tissue in question.

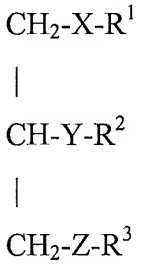
44. (Previously Presented) The method according to claim 43, wherein the drug delivery system becomes located in diseased tissue after administration and, after degradation by extracellular phospholipase A2, leads to an increase in membrane permeability of cells in the diseased tissue.

45. (Previously Presented) The method according to claim 43, wherein the drug delivery system includes a second drug substance, a membrane component, and/or an auxiliary drug substance which acts as an proactivator for extracellular phospholipase A2.

46. (Previously Presented) The method according to claim 43, wherein the drug delivery system becomes located in a diseased tissue after administration, and wherein degradation of the drug delivery system by extracellular phospholipase A2 in the diseased tissue is accelerated by a localized increase in temperature in said tissue.

47. (Original) The method according to claim 38, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions and cancer.

48. (Original) A lipid derivative of the following formula:



wherein

X and Z independently are selected from O, CH_2, NH, NMe, S, S(O), and $S(O)_2$;

Y is -OC(O)-, Y then being connected to R^2 via either the oxygen or carbonyl carbon atom;

R^1 is an aliphatic group of the formula Y^1Y^2;

R^2 is an organic radical having at least 7 carbon atoms;

where Y^1 is $-(CH_2)_{n1}-(CH=CH)_{n2}-(CH_2)_{n3}-(CH=CH)_{n4}-(CH_2)_{n5}-(CH=CH)_{n6}-(CH_2)_{n7}-(CH=CH)_{n8r}-(CH_2)_{n9}$, and the sum of n1+2n2+n3+2n4+n5+2n6+n7+2n8+n9 is an integer of from 9 to 29; n1 is zero or an integer of from 1 to 29, n3 is zero or an integer of from 1 to 20, n5 is zero or an integer of from 1 to 17, n7 is zero or an integer of from 1 to 14, and n9 is zero or an integer of from 1 to 11; and each of n2, n4, n6 and n8 is independently zero or 1; and Y^2 is CH_3 or CO_2H; where each Y^1-Y^2 independently may be substituted with halogen or C_{1-4}-alkyl,

R^3 is selected from derivatives of phosphatidic acid to which a hydrophilic polymer is attached.

49. (Previously Presented) The lipid derivative according to claim 48, wherein the hydrophilic polymer is selected from polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatized celluloses.

50. (Previously Presented) The lipid derivative according to claim 48, wherein X and Z are O.

51. (Previously Presented) The lipid derivative according to claim 48, wherein X and Z are O, R^1 and R^2 are independently selected from alkyl groups, $(CH_2)_nCH_3$, where n is 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29; Y is -OC(O)-, Y then being connected to R^2 via the carbonyl carbon atom.

52. (Previously Presented) The pharmaceutical composition comprising the lipid derivative according to claim 48 and optionally a pharmaceutically acceptable carrier.

53. (Previously Presented) The pharmaceutical composition according to claim 52, wherein the lipid derivative is dispersed in the form of a liposome or a micelle.

54. (Previously Presented) The method of treating a mammal by administering to the mammal in need thereof an efficient amount of the lipid derivative defined in claim 48.

55. (Original) The use according to claim 54, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions, and cancer.

56. (Original) The use according to claim 55, wherein the type of cancer is selected from the group consisting of brain cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, leukemia, lymphoma, sarcoma and carcinoma.

57. (Previously Presented) A lipid-based drug delivery system for administering an active lysolipid drug substance, which is not a substrate for lysophospholipase, to tissues expressing increased levels of extracellular phospholipase A2, comprising:

(a) a prodrug lipid derivative having the formula:

CH_2-O-R^A
|
CH-O-R^B

|

CH_2-O-R^C

wherein R^A is an ether-linked fatty acid chain having at least 7 carbon atoms, R^B is an acyl-linked fatty acid chain having at least 7 carbon atoms and R^C is chosen from the group consisting of phosphatidic acid, phosphatidyl choline, phosphatidyl glycerol and phosphatidyl serine; and

(b) at least one lipopolymer or glycolipid.

58. (Previously Presented) The lipid based drug delivery system according to claim 57, wherein the lipopolymers or glycolipids are represented by at least a fraction of the prodrug lipid derivative.

59. (Previously Presented) The lipid-based drug delivery system according to claim 57, wherein the the polymer of the lipopolymer is selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatized celluloses.

60. (Previously Presented) The lipid-based drug delivery system according to claim 57, wherein the lipid-based system is in the form of liposomes .

61. (Previously Presented) The lipid-based drug delivery system according to claim 57, which is in the form of liposomes wherein a second drug substance is incorporated.

62. (Previously Presented) The lipid-based drug delivery system according to claim 57, wherein the second drug substance is a therapeutically and/or prophylactically active substance selected

from the group consisting of (i) antitumor agents, (ii) antibiotics and antifungals and (iii) anti-inflammatory agents.

63. (Previously Presented) A pharmaceutical composition comprising the lipid-based drug delivery system according to claim 57 and optionally a pharmaceutically acceptable carrier.

64. (Previously Presented) A method for selectively drug targeting to neoplastic cells within a mammalian body having a extracellular phospholipase A2 activity which is at least 25% higher compared to the normal activity in said areas, by administering to the mammal in need thereof an efficient amount of the lipid-based drug delivery system according to claim 57.

65. (Previously Presented) A method of treating a mammal by administering to the mammal in need thereof an effective amount of the lipid-based drug delivery system according to claim 57.

66. (Previously Presented) The method according to claim 64 for the treatment of diseases or conditions associated with a localized increase in extracellular phospholipase A2 activity in mammalian tissue.

67. (Previously Presented) The method according to claim 66, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions and cancer.

68. (Previously Presented) The method according to claim 67, wherein the type of cancer is selected from the group consisting of brain cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, leukemia, lymphoma, sarcoma and carcinoma.

69. (Previously Presented) The method according to claim 64, wherein the increase in extracellular phospholipase A2 activity is a least 25% compared to the normal level of activity in the tissue in question.

70. (Previously Presented) The method according to any one of claims 15, 16, 38, 39, 54 or 65, wherein the mammal is a human.

71. (Previously Presented) A liposomal drug delivery system for administering an active lysolipid drug substance, which is not a substrate for lysophospholipase, to tissues expressing increased levels of extracellular phospholipase A2, comprising:

(a) a prodrug lipid derivative having the formula:

CH_2-X-R^1
|
CH-Y-R^2
|
CH_2-Z-R^3

wherein
X and Z independently are selected from O, CH_2, NH, NMe, S, S(O), and $S(O)_2$;
Y is -OC(O)-, Y then being connected to R^2 via either the oxygen or carbonyl carbon atom;
R^1 is an aliphatic group of the formula Y^1Y^2; where Y^1 is $-(CH_2)_{n1}-(CH=CH)_{n2}-(CH_2)_{n3}-(CH=CH)_{n4}-(CH_2)_{n5}-(CH=CH)_{n6}-(CH_2)_{n7}-(CH=CH)_{n8r}-(CH_2)_{n9}$, and the sum of n1+2n2+n3+2n4+n5+2n6+n7+2n8+n9 is an integer of from 9 to 29; n1 is zero or an integer of from 1 to 29, n3 is zero or an integer of from 1 to 20, n5 is zero or an integer of from 1 to 17, n7 is zero or an integer of from 1 to 14, and n9 is zero or an integer of from 1 to 11; and each of n2, n4, n6 and n8 is independently zero or 1; and Y^2 is CH_3 or CO_2H; where each Y^1-Y^2 independently may be substituted with halogen or C_{1-4}-alkyl,
R^2 an alkyl group $(CH_2)_nCH_3$ where n is any one of 11-29; and
R^3 is chosen from the group consisting of phosphatidic acid, phosphatidyl choline, phosphatidyl glycerol and phosphatidyl serine; and

(b) at least one phospholipid with covalently linked polymers or polysaccharides.

72. (Previously Presented) A liposomal drug delivery system for administering an active lysolipid drug substance, which is not a substrate for lysophospholipase, to tissues expressing increased levels of extracellular phospholipase A2, comprising:

(a) a prodrug lipid derivative having the formula:

CH_2-X-R^1
|
CH-Y-R^2
|
CH_2-Z-R^3

wherein
X and Z are O;
Y is -OC(O)-, Y then being connected to R^2 via either the oxygen or carbonyl carbon atom;
R^1 and R^2 are each independently an alkyl group $(CH_2)_nCH_3$, where n is any one of 11-29; and
R^3 is chosen from the group consisting of phosphatidic acid, phosphatidyl choline, phosphatidyl glycerol and phosphatidyl serine; and

(b) at least one phospholipid with covalently linked polymers or polysaccharides.

73. (New) The drug delivery system according to claim 5, wherein X and Z are each O.

74. (New) A method for selectively drug targeting to neoplastic cells within a mammal having an extracellular phospholipase A2 activity which is at least 25% higher compared to the normal activity in said areas, by administering to the mammal in need thereof an efficient amount of the lipid-based drug delivery system according to claim 73.